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entry Q53653

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Entry information

Entry name	Q53653_STAAU
Primary accession number	Q53653
Secondary accession numbers	None
Entered in TrEMBL in	Release 01, November 1996
Sequence was last modified in	Release 01, November 1996
Annotations were last modified in	Release 26, March 2004
Name and origin of the protein	
Protein name	Clumping factor
Synonyms	None
Gene name	None
From	Staphylococcus aureus [TaxID: 1280]
Taxonomy	Bacteria; Firmicutes; Bacillales; Staphylococcus.

References

[1] NUCLEOTIDE SEQUENCE.

STRAIN=Newman;

MEDLINE=94224142; PubMed=8170386 [NCBI, ExPASy, EBI, Israel, Japan]

McDevitt D., Francois P., Vaudaux P., Foster T.J.;

"Molecular characterization of the clumping factor(fibrogen receptor of Staphylococcus aureus.";
Mol. Microbiol. 11:237-248(1994).

Comments

None

Cross-references

EMBL	Z18852; CAA79304.1; -; Genomic_DNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S41539; S41539.	
PDB	1N67; X-ray; A=221-559.	[ExPASy / RCSB / EBI]
	GO:0009986; Cellular component: cell surface (<i>inferred from electronic annotation</i>).	
GO	GO:0005618; Cellular component: cell wall (<i>inferred from electronic annotation</i>).	
	GO:0016020; Cellular component: membrane (<i>inferred from electronic annotation</i>).	
	QuickGo view.	
InterPro	IPR005877; Gpos_YsIRK. IPR001899; Gram_pos_anchor.	

Graphical view of domain structure.

Pfam PF00746; Gram_pos_anchor; 1.
PF04650; YSIRK_signal; 1.
Pfam graphical view of domain structure.

TIGRFAMs TIGR01167; LPXTG_anchor; 1.

PROSITE PS50847; GRAM_POS_ANCHORING; 1.
PROSITE graphical view of domain structure (profiles).

ProDom [Domain structure / List of seq. sharing at least 1 domain]

HOGENOM [Family / Alignment / Tree]

ProtoMap Q53653.

PRESAGE Q53653.

ModBase Q53653.

SWISS-2DPAGE Get region on 2D PAGE.

UniRef View cluster of proteins with at least 50% / 90% identity.

Keywords**Cell wall.****Features**

None

Sequence information

Length: 933 AA Molecular weight: 97057 Da CRC64: EB51A6DE2FF759F4 [This is a checksum on the sequence]

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<u>70</u>	<u>80</u>	<u>90</u>	<u>100</u>	<u>110</u>	<u>120</u>
SVSAAPKTDD	TNVSDTKTSS	NTNNGETSVA	QNPAQQETTQ	SSSTNATTEE	TPVTGEATTT
<u>130</u>	<u>140</u>	<u>150</u>	<u>160</u>	<u>170</u>	<u>180</u>
TTNQANTPAT	TQSSNTNAEE	LVNQTSNETT	FNDTNTVSSV	NSPQNSTNAE	NVSTTQDTST
<u>190</u>	<u>200</u>	<u>210</u>	<u>220</u>	<u>230</u>	<u>240</u>
EATPSNNEA	PQSTDASNKD	VVNQAVNTSA	PRMRAFSLAA	VAADAPAAGT	DITNQLTNVT
<u>250</u>	<u>260</u>	<u>270</u>	<u>280</u>	<u>290</u>	<u>300</u>
VGIDSGTTVY	PHQAGYVKLN	YGFSVPNSAV	KGDTFKITVP	KELNLNGVTS	TAKVPPIMAG
<u>310</u>	<u>320</u>	<u>330</u>	<u>340</u>	<u>350</u>	<u>360</u>
DQVLANGVID	SDGNVIYTFT	DYVNTKDDVK	ATLTMPAYID	PENVKKTGNV	TLATGIGSTT
<u>370</u>	<u>380</u>	<u>390</u>	<u>400</u>	<u>410</u>	<u>420</u>
ANKTVLVDE	KYGKFYNLSI	KGTIDQIDKT	NNTYRQTIYV	NPSGDNVIAP	VLTGNLKPNT
<u>430</u>	<u>440</u>	<u>450</u>	<u>460</u>	<u>470</u>	<u>480</u>
DSNALIDQQN	TSIKVYKVDN	AADLSESYFV	NPENFEDVTN	SVNITFPNPN	QYKVEFNTPD
<u>490</u>	<u>500</u>	<u>510</u>	<u>520</u>	<u>530</u>	<u>540</u>
DQITTPYIVV	VNGHIDPNSK	GDLALRSTLY	GYNSNIIWRS	MSWDNEVAFN	NGSGSGDGID
<u>550</u>	<u>560</u>	<u>570</u>	<u>580</u>	<u>590</u>	<u>600</u>
KPVVPEQPDE	PGEIEPIPED	SDSDPGSDSG	SDSNSDSGSD	SGSDSTSDSG	SDSASDSDSA

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      910      920      930
SEDEANTSLI WGLLASIGSL LLFRRKKENK DKK

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Dan Med Bull. 1987 Apr;34(2):59-69.

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Interactions between human plasma proteins and cell wall components of *Staphylococcus aureus*.

Espersen F.

Staphylococcus aureus has surface structures with affinity to human IgG, fibrinogen, and fibronectin. Besides the binding of the Fc-terminal part of IgG from a range of mammalian species, *S. aureus* protein A binds some IgM, IgA, and IgE molecules. Furthermore, it seems also able to bind immunoglobulins via their Fab-terminal parts. Protein A (Mr 42,000) is the only well-characterized *S. aureus* cell wall protein, and its structure is known in detail. A considerable number of biological properties of protein A has been demonstrated. Most of these properties seem to be a consequence of the complement activation induced by protein A-IgG complexes. The role of protein A in the phagocytosis of *S. aureus* is complex. By complement consumption protein A has been found to inhibit the phagocytosis of staphylococci by polymorphonuclear leucocytes. However, it has been demonstrated that protein A-containing staphylococci bind to surface IgG on human alveolar and peritoneal macrophages and thereby promote phagocytosis by these cells. This phenomenon might explain the increased virulence of *S. aureus* in the presence of human IgG in experimental peritonitis in mice. Fibrinogen binds to a surface structure on *S. aureus*, designated clumping factor as the binding results in clumping of whole bacteria. Recently, a glycoprotein (Mr of about 400,000) has been isolated from *S. aureus*. This glycoprotein seems to be the clumping factor. It binds to fibrinogen, inhibits the fibrinogen induced clumping, and seems to be a *S. aureus* specific, surface component. The isolated component activates human complement in vitro. Also, it induces protection against *S. aureus* peritonitis in immunized mice. The presence of fibrinogen and an unknown human plasma component increases the virulence of *S. aureus* in experimental peritonitis in mice, but the role of fibrinogen in human *S. aureus* infection is unknown. Fibronectin binds to a surface protein on *S. aureus*, and this binding also results in the clumping of the bacteria. The binding site(s) for fibronectin is different from the binding sites for fibrinogen and IgG. A fibronectin-binding protein (Mr 197,000) has been isolated from *S. aureus* by affinity chromatography. This protein binds fibronectin and inhibits the fibronectin induced *S. aureus* clumping. No other biological properties of this protein have yet been demonstrated. The binding of fibronectin to *S. aureus* opsonize the bacteria for polymorphonuclear leucocytes. The opsonic capacity is, however, low compared to other serum opsonins. It has been suggested that fibronectin plays a role in the attachment of *S. aureus*, but further studies are needed.(ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:

FEMS Microbiol Lett. 1994 May 15;118(3):199-205.

[Related Articles](#), [Links](#)

Surface-associated proteins of *Staphylococcus aureus*: their possible roles in virulence.

Foster TJ, McDevitt D.

Microbiology Department, Moyne Institute, Trinity College, Dublin, Ireland.

A class of proteins that are associated with the cell surface of Gram-positive bacteria has been recognised. Common structural features which are implicated in the proper secretion and attachment of these proteins to the cell surface occur in the C-termini. N-terminal domains interact with the host by binding to soluble host proteins, to matrix proteins or to host cells. They probably have important roles in pathogenicity by allowing bacteria to avoid host defences and by acting as adhesins. Four such proteins of *Staphylococcus aureus* have been characterised: protein A (immunoglobulin binding protein), fibronectin binding proteins, collagen binding protein and the fibrinogen binding protein (clumping factor). Site-specific mutants are being used to define their roles in pathogenesis in in vitro and in vivo models of adherence and infection.

Publication Types:

- Review

(6) Synergistic activity with antibiotics

TABLE 2

Metabolic Properties of Immunglobulins					
	IgG	IgA	IgM	IgD	IgE
Serum Level	989	200	100	3	0.008
Mean (mg/dl)	(600-1600)	(60-330)	(45-150)		
Total Body Pool	1030	210	36	1.1	0.01
mean (mg/kg)	(570-2050)				
Synthesis rate	36	28	2.2	0.4	0.004
mean (mg/kg/day)					
Plasma half life	21	5.9	5.1	2.8	2.4
mean (days)					
Fractional turn-over rate	6.9	24.0	10.6	37.0	72.0
(% day) mean					
Fraction for each class in plasma* mean	0.52	0.55	0.74	0.75	0.51

*This fraction represents the portion of the total immunoglobulins of each class that is found in the plasma.

Host responses are initiated only after bacteria or viruses have already colonized tissues or implants and are beginning to enhance their own defenses (antigen masking, replication, biofilm, toxins). The host defense strategies require time to reach peak responses. During this time period, serious infection may be established, especially in immunocompromised patients. The presence of tissue damage and foreign bodies lower thresholds of infection and diminishes effective responses.

In the last decade, intravenous immunoglobulins (IVIG) have become a major treatment regime for bacterial and viral infections and of primary and secondary immunodeficiency states. For example, Buckley et al., *New Eng. J. Med.* 325:110-117 (1991), describe using intravenous immune globulin in the treatment of immunodeficiency diseases, and Cometta et al., *New Eng. J. Med.* 327:234-239 (1992), describe the prophylactic intravenous administration of standard immune globulin and core-lipopolysaccharide immune globulin in patients at high risk of post-surgical infection. IVIGs are prepared from the pooled plasmas of large numbers of donors, and tend to have a broad representation of antibodies. Specifically, pooled polyvalent human globulins usually contain antibodies for ubiquitous pathogens such as *H. influenza* type b, pneumococci, staphylococci, diphtheria, tetanus, respiratory syncytial virus (RSV), measles, cytomegalovirus (CMV), and varicella zoster virus. Antibody concentrations from lot to lot and from manufacturer to manufacturer usually vary only two to four fold when measured by antibody binding assays. However, functional assays often show much larger lot to lot variations as do antibody concentrations to less common pathogens (see, Siber et al., "Use of immune globulins in the prevention and treatment of infections", *Current Clinical Topics in Infectious Disease*, Remington J S, Swartz M M, eds., Blackwell Scientific, Boston, 12:208-257 (1992)).

IVIG therapy has been reported to be beneficial for more than thirty five diseases produced by immunopathologic mechanisms. Passive immunization against infections has been particularly successful with immune globulins specific for tetanus, hepatitis B, rabies, chickenpox, and cytomegalovirus. Passive immunization depends on the presence of high and consistent titers of antibodies to the respective pathogens in each preparation.

Nosocomial infections are derived from the hospital or clinical setting, and are also a serious problem. Specifically,

bacteria and viruses present in the hospital or clinic can infect a recovering patient and put the patient at risk or prolong the recovery period. A patient's risk factors for nosocomial infection can be intrinsic, such as susceptibility to infection due to immunosuppression, or extrinsic, such as invasive medical interventions (e.g., surgery or use of medical devices such as catheters, ventilators, etc.). *Staphylococcus aureus* is an important cause of nosocomial infection, especially nosocomial pneumonia, surgical wound infection, and bloodstream infection (Panlilio et al., *Infect. Cont. Hosp. Epidemiol.* 13:582-586 (1992)). Other pathogens commonly associated with nosocomial infection include, but are not limited to, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus spp.*, *Enterobacter spp.*, coagulase-negative staphylococci (CNS), and *Candida albicans* (Emori et al., *Am. J. Med.* 91: (suppl 3B) 289S-293S (1991)). Hospitals and clinics typically employ strict sterilization procedures and use antibiotics such as methicillin, oxacillin, and nafcillin to combat virulent bacterial pathogens. However, nosocomial infections still occur in great numbers and are expected to increase with an aging population.

The use of intravenous immunoglobulins to prevent nosocomial infections has been discussed in Siber, *New Eng. J. Med.* 327:269-271 (1992). Passive immunization against infections has been particularly successful using immune globulins containing antibodies specific for tetanus, hepatitis B, rabies, chickenpox, and CMV. However, it is reported that there is an inconsistent benefit from using intravenous immune globulins to prevent nosocomial infections. This may be due to variable lot-to-lot levels of antibodies to the more common nosocomial pathogens and emerging new serotypes.

U.S. Pat. No. 4,412,990 to Lundblad et al. discloses an intravenous pharmaceutical composition containing immunoglobulin (IgG) and fibronectin that exhibits a synergistic opsonic activity which results in enhanced phagocytosis of bacteria, immune complexes, and viruses.

U.S. Pat. No. 4,994,269 to Collins et al. discloses the topical use of monoclonal antibodies for the prevention and treatment of experimental *P. aeruginosa* lung infections. Specifically, the antibodies are administered via aerosol spray to the lungs. Results show beneficial effects in the treatment of *Pseudomonas pneumonia*.

U.S. Pat. No. 4,714,612 to Nakamura et al. discloses the use of a non-specific gamma globulin IgG in a mouthwash for preventing gingivitis. Ma et al., *Arch. Oral Biol.* 35 suppl:115S-122S, 1990, discloses the use of monoclonal antibodies specific for *Streptococcus mutans* in a mouthwash. Experiments showed control subjects experienced recolonization with *Streptococcus mutans* within two days, but those treated with the monoclonal antibodies remained free of *Streptococcus mutans* for up to two years.

SUMMARY OF THE INVENTION

It is an object of this invention to provide a new method for the direct, concentrated local delivery of passive immunity.

It is another object of this invention to provide new compositions which include a full repertoire of immunoglobulin classes (IgG, IgA, IgM), and new methods for prophylactic positioning of the compositions wherein the compositions are applied directly to wounds, burns, tissues, and biomaterial devices as a creme, ointment, coating, layer, or the like, to prevent and treat infection from microorganisms and viruses.

It is another object of this invention to provide new compositions, which can include a full repertoire of immu-

noglobulin classes (IgG, IgA, IgM), and has a broad spectrum of antibodies with elevated antibody titers to specific microorganisms that commonly cause biomaterial, burn, mucosal, tissue, surgical wound, and body cavity infections.

It is another object of this invention to provide a biocompatible layer with an immunoglobulin composition containing a broad spectrum of antibodies to specific infectious pathogens immobilized thereon that is placed in-situ in the treatment of wounds and burns.

It is another object of this invention to coat catheters and the like, which are used for acute or chronic treatment, with a composition containing a broad spectrum of immunoglobulins which includes antibodies to prevent the types of infections which often result with the long term use of these devices.

It is another object of this invention to provide a method of using immunoglobulin compositions of broad spectrum and high concentration, whereby bacteria are pre-opsonized in-situ for enhanced phagocytosis and killing.

According to the invention, the direct, concentrated local delivery of passive immunity is accomplished by applying a composition having a full repertoire of immunoglobulins (IgG, IgM and IgA) to biomaterials, implants, tissues, and wound and burn sites. The composition preferably has elevated concentrations of certain immunoglobulin classes (IgG, IgM, and IgA), and elevated antibody titers to specific microorganisms that commonly cause biomaterial, burn, mucosal, tissue, surgical wound, and body cavity infections. Compositions within the practice of this invention may take several forms, including cremes, gels, ointments, lavage fluids, sprays, lozenges, coatings, layers, or any other topical mode of administration. In addition, the compositions may be combined with or immobilized on a biocompatible or biodegradable material, or be impregnated in a matrix material for sustained release. The compositions can be used for both prevention and treatment of infections.

In oral applications, the composition would ideally be provided as a lozenge, mouthwash, or spray, while in trauma patients the composition may be best applied as a creme or ointment, or as part of a biomaterial implant or fixation device. The immunoglobulins and other antibodies of the present compositions can be immobilized on a biocompatible material which is placed in-situ in a patient's wound or burn site, or be coated on a catheter or the like that is inserted in a body cavity.

Application of the compositions should occur within six hours or at a time of trauma or of cleaning the wound or burn site so that bacteria present therein or arriving at the site will be pre-opsonized for phagocytosis and killing prior to their replication and potential toxin production. Furthermore, application prior to biofilm formation reduces the adhesion of infectious bacteria to biomaterial implants and certain tissues, and helps prevent the formation of a biofilm which would block contact of the infectious bacteria with circulating immunoglobulins and macrophages.

In summary, tissue, wound or biomaterial surface pre-treatment at the time of surgery or shortly after trauma, would allow the effective use of a full repertoire of immunoglobulins, including IgG, IgM, and IgA at high concentrations without side effects, before colonization and infection develops.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

It is well established that the microorganisms that are causative agents of biomaterial-related infections have a

strong affinity for binding to the surfaces of biomaterials (See, Gristina et al., "Materials, Microbes and Man: The Problem of Infection Associated with Implantable Devices", *Current Perspectives on Implantable Devices*, Vol. 1, pp. 71-137 (1989), JAI Press, Inc.). This affinity allows these causative agents of serious biomaterial related infections to colonize the surfaces of biomaterials. At the moment of implantation, a polymeric biomaterial, such as a vascular graft or the like, is a ready site for competitive bacterial or tissue colonization. In vivo, available bacteria may defeat the host tissue cells in a race for the polymer's surface and thus cause infection, resulting in the failure of tissue integration, of the polymer (Gristina et al., *Zbl. Bakt. Suppl.* 16, Gustav Fischer Verlag, Stuttgart, New York, pp. 143-157 (1987)). Bacteria colonized on the surface of a biomaterial become protected from antibiotics and host defenses (immunoglobulins) by a biofilm and continuously maintain the infection in the patient, despite antibiotic medication. The biofilm also provides the bacteria with some protection from phagocytes, a major mechanism of host defense. Experience has shown that phagocytes have great difficulty in their attempts to phagocytose and kill the offending organisms growing at the biomaterial-host tissue interface, particularly when bacteria are embedded in a biofilm.

Experiments have shown that hyperimmune sera made in rabbits by injecting rabbits with killed *Staphylococcus epidermidis* (RP12 strain) and/or the polysaccharide capsular slime extracted from *S. epidermidis* strain RP12 markedly reduces the adherence of the RP12 strain to the surface of the biomaterial polymethylmethacrylate (PMMA). *S. epidermidis*, which is usually thought of as a nonpathogenic commensal human skin saprophyte, has emerged as a serious pathogen in biomaterial-related infections as well as in immunocompromised patients (Gristina et al., *Zbl. Bakt. Suppl.* 16, Gustav Fischer Verlag, Stuttgart, New York, pp. 143-157 (1987)). In these experiments, standard suspensions of the RP12 strain of *S. epidermidis* were incubated for thirty minutes with 1:200 dilutions of either normal rabbit serum or hyperimmune serum against the RP12 strain of *S. epidermidis*. This allowed the specific antibodies to bind to the surface polysaccharide molecules of the organisms. These suspensions were washed with phosphate buffered saline (PBS) and standard samples of PMMA were added to the various preparations. The bacteria-PMMA preparations were incubated for sixty minutes, and the PMMA samples were then washed three times with PBS to remove loosely attached bacteria. The PMMA samples were sonicated for ten minutes in PBS and the supernatants were diluted and plated on Trypticase-Soy agar to determine the number of colony forming units (CFU) that adhered to the PMMA samples. Table 3 presents the experimental results.

TABLE 3

Effect of Anti-RP12 Antisera on the Binding of the
RP12 Strain of *S. epidermidis* to PMMA

PMMA plus RP12 incubated with	CFU Bound to PMMA	Percent inhibition
PBS	393,000	
Normal Serum (1:200)	319,000	
Antiserum (1:200; lot 11949)	105,000	67* 73*

*Calculated as the percent inhibition of anti-sera treated RP12 versus RP12 pretreated with normal sera.

*Calculated as the percent inhibition of anti-sera-treated RP12 versus RP12 pretreated with only PBS.

Table 3 shows that normal serum has some inhibitory effects. This is not surprising because a low level of antibody

13733663 PMID: 11393292

Isolation and characterisation of a 17-kDa staphylococcal heparin-binding protein with broad specificity.

Fallgren C; Utt M; Ljungh A

Department of Infectious Diseases and Medical Microbiology, University of Lund, Sweden.

Journal of medical microbiology (England) Jun 2001, 50 (6) p547-57,

ISSN 0022-2615 Journal Code: 0224131

Publishing Model Print

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Languages: ENGLISH

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Subfile: INDEX MEDICUS

A previous study reported the ability of staphylococci to bind heparin and heparin-dependent host growth factors. The present study isolated and identified heparin- and basic fibroblast growth factor (bFGF)-binding surface components of *S. epidermidis* strain **RP12** and *S. haemolyticus* strain SM 131. The staphylococcal heparin-binding component(s) were purified by affinity chromatography on heparin-Sepharose and a major heparin-binding protein, here designated HBP, was identified by immunoblot in these two coagulase-negative staphylococcal (CNS) species. The HBP was shown to be acidic with an approximate pI of 4.6 and a molecular mass around 17 kDa. The binding of heparin to HBP was inhibited by heparin, fucoidan, pentosan polysulphate and various other sulphated polysaccharides, but not by non-sulphated compounds. However, the purified HBP from both *S. epidermidis* and *S. haemolyticus* revealed broad specificity, and also bound bFGF, thrombospondin, von Willebrand factor and, weakly, fibrinogen. The N-terminal sequences of the 17-kDa HBP from *S. epidermidis* and *S. haemolyticus* showed only limited identity. Comparison of the first 15 amino acid residues derived from either strain with known sequences in the protein databases revealed no close similarities. Taken together, these results suggest that the **adhesion** of at least some CNS to host sulphated glycosaminoglycans may be mediated by a previously uncharacterised group of surface proteins.

Tags: Research Support, Non-U.S. Gov't

Descriptors: *Bacterial Outer Membrane Proteins; *Carrier Proteins --isolation and purification--IP; *Fibroblast Growth Factor 2--isolation and purification--IP; *Heparin--metabolism--ME; * **Staphylococcus** --metabolism--ME; Amino Acid Sequence; Autoradiography; Carrier Proteins --chemistry--CH; Carrier Proteins--metabolism--ME; Electrophoresis, Gel, Two-Dimensional; Electrophoresis, Polyacrylamide Gel; Fibroblast Growth Factor 2--classification--CL; Fibroblast Growth Factor 2--metabolism--ME; Hydrogen-Ion Concentration; Immunoblotting; Membrane Proteins; Molecular Sequence Data; Polysaccharides, Bacterial--metabolism--ME; Protein Binding

Molecular Sequence Databank No.: GENBANK/AF169242

CAS Registry No.: 0 (17-kDa HBP protein, *Staphylococcus*); 0 (Bacterial Outer Membrane Proteins); 0 (Carrier Proteins); 0 (Membrane Proteins); 0 (Polysaccharides, Bacterial); 103107-01-3 (Fibroblast Growth Factor 2); 9005-49-6 (Heparin)

Record Date Created: 20010606

Record Date Completed: 20010621

13/9/2

DIALOG(R) File 155:MEDLINE(R)

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12224605 PMID: 9532261

In vitro anti-staphylococcal activity of heparinized biomaterials bonded with combinations of rifampicin.

Fallgren C; Utt M; Petersson A C; Ljungh A; Wadstrom T

Department of Medical Microbiology, University of Lund, Sweden.

Zentralblatt fur Bakteriologie - international journal of medical microbiology (GERMANY) Jan 1998, 287 (1-2) p19-31, ISSN 0934-8840

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Document type: Journal Article

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Record type: MEDLINE; Completed

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Biomaterial implants in various human body tissues are highly susceptible to bacterial **colonization**. We report here on the coating of heparinized biomaterials with heparin binding extracellular matrix proteins giving special regard to the efficient adsorption and slow release of antibiotics. Heparin was partially degraded and the resulting fragments were covalently end-point **attached** to 0.5 cm long silicone biomaterial surface. Collagen type I was immobilized on the heparinized biomaterials and then cross-linked with acyl-azide or carbodiimide. Finally, the resulting biosurfaces were exposed to antibiotics, i.e. rifampicin in combination with cefuroxime, fusidic acid, ofloxacin or vancomycin, respectively. The antibiotic bonded biomaterials were evaluated for their anti-staphylococcal activity after elution in NaCl, serum or blood by measuring the zones of inhibition for *S. epidermidis* strain **RP12**. Furthermore, we examined the in-vitro **colonization** resistance to *S. epidermidis* **RP12** for these combinations of rifampicin-bonded biomaterials by an ATP bioluminescence assay. The ATP measurements showed that initially **adherent** bacteria were eradicated from the polymer surface, for at least 24 or 48 h (fusidic acid > cefuroxime > vancomycin > ofloxacin). The anti-staphylococcal activity of rifampicin-fusidic acid bonded heparinized biomaterials seems of sufficient duration and efficacy to merit testing in an animal model.

Tags: Research Support, Non-U.S. Gov't

Descriptors: *Anti-Bacterial Agents--pharmacology--PD; *Biocompatible Materials; *Collagen--pharmacology--PD; *Rifampin--pharmacology--PD; Cefuroxime--metabolism--ME; Cefuroxime--pharmacology--PD; Collagen--drug effects--DE; Collagen--metabolism--ME; Fusidic Acid--metabolism--ME; Fusidic Acid--pharmacology--PD; Ofloxacin--metabolism--ME; Ofloxacin--pharmacology--PD; Rifampin--metabolism--ME; **Staphylococcus epidermidis**--drug effects--DE; **Staphylococcus epidermidis**--pathogenicity--PY; Vancomycin--metabolism--ME; Vancomycin--pharmacology--PD

CAS Registry No.: 0 (Anti-Bacterial Agents); 0 (Biocompatible Materials); 13292-46-1 (Rifampin); 1404-90-6 (Vancomycin); 55268-75-2 (Cefuroxime); 6990-06-3 (Fusidic Acid); 82419-36-1 (Ofloxacin); 9007-34-5 (Collagen)

Record Date Created: 19980407

Record Date Completed: 19980407

13/9/3

DIALOG(R) File 155:MEDLINE(R)

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11167291 PMID: 8541809

Biomaterial-associated staphylococcal peritoneal infections in a neutropaenic mouse model.

Rozalska B; Ljungh A

Gristina, Science 237:1588-1595 (1987), points out that inhibiting bacterial adhesion is an important parameter in reducing biomaterial-centered infection.

Paulsson, M., .ANG.. Ljungh, and T. Wadstrom. 1992. Rapid identification of fibronectin, vitronectin, laminin, and collagen cell surface binding proteins on coagulase-negative staphylococci by particle agglutination assays [see comments]. J Clin Microbiol. 30:2006-12.

Department of Infectious Biology, University of Lodz, Poland.
FEMS immunology and medical microbiology (NETHERLANDS) Jul 1995, 11
(4) p307-19, ISSN 0928-8244 Journal Code: 9315554
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS

Adhesion of staphylococcal cells to polyethylene with end point-**attached** heparin was quantified by bioluminescence. **Staphylococcus** epidermidis 3380 and the slime-producing *S. epidermidis* **RP12** **adhered** to the highest extent, and *S. lugdunensis* 2342 to the least extent. Preincubation of the polymer with dialysis fluid reduced **adhesion** of *S. epidermidis* 3380 and **RP12** but enhanced that of *S. aureus*, and preadsorption of the surface with fibronectin decreased subsequent **adhesion** of *S. epidermidis* and *S. haemolyticus* strains. When staphylococci were grown in the presence of a biomaterial their ability to activate peritoneal cells was decreased. The bactericidal activity was impaired, whereas ingestion of opsonized coagulase-negative staphylococci (CNS) strains was unaffected. With *S. epidermidis* **RP12** the presence of biomaterial did not influence either phagocytosis or bactericidal effect of peritoneal cells. After intra-peritoneal challenge with staphylococcal strains, the organ uptake of *S. aureus* Cowan 1 was increased in normal mice whereas immunosuppressed mice died. CNS strains increased mainly in the peritoneal cavity of immunosuppressed mice. The uptake of bacteria in liver and kidneys was increased with *S. epidermidis* 3380, *S. lugdunensis* 2343 and *S. schleiferi* 667-88. Generally, CNS strains persisted in the peritoneal cavity of both normal and immunosuppressed mice. These data indicate that host defense mechanisms, mainly polymorphonuclear neutrophils, fail to eliminate CNS infections in the peritoneum, and that initial **adhesion** to an implanted biomaterial may be of lesser importance in the peritoneal cavity than in e.g. catheter-associated infections. There are strain-specific virulence factors of bacteria, and slime producing strains evade the host defense mechanisms more efficiently than non-slime producing strains.

Tags: Comparative Study; Female; Male; Research Support, Non-U.S. Gov't

Descriptors: *Neutropenia--immunology--IM; *Peritonitis--etiology--ET; *Prostheses and Implants--adverse effects--AE; *Staphylococcal Infections--etiology--ET; * **Staphylococcus** --pathogenicity--PY; Adsorption; Animals; Ascitic Fluid; Bacterial **Adhesion** --drug effects--DE; Coagulase--analysis--AN; Disease Susceptibility--immunology--IM; Fibronectins--pharmacology--PD; Heparin; Immunocompromised Host; Kidney--microbiology--MI; Liver--microbiology--MI; Mice; Mice, Inbred DBA; Neutropenia--complications--CO; Neutrophils--immunology--IM; Peritoneal Cavity--cytology--CY; Peritoneal Dialysis; Peritonitis--immunology--IM; Phagocytosis; Polyethylenes; Polysaccharides, Bacterial--metabolism--ME; Species Specificity; Staphylococcal Infections--immunology--IM; **Staphylococcus** --physiology--PH; **Staphylococcus aureus**--physiology--PH; **Staphylococcus epidermidis**--physiology--PH; Tissue Distribution

CAS Registry No.: 0 (Coagulase); 0 (Fibronectins); 0 (Polyethylenes); 0 (Polysaccharides, Bacterial); 9005-49-6 (Heparin)

Record Date Created: 19960213

Record Date Completed: 19960213

13/9/4

DIALOG(R) File 155:MEDLINE(R)

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10834629 PMID: 7829558

Inhibition of Staphylococcus adherence to biomaterials by extracellular slime of S. epidermidis RP12 .

Giridhar G; Kreger A S; Myrvik Q N; Gristina A G

Medical Sciences Research Institute, Herndon, Virginia 22070.

Journal of biomedical materials research (UNITED STATES) Nov 1994, 28 (11) p1289-94, ISSN 0021-9304 Journal Code: 0112726

Contract/Grant No.: AR 26957; AR; NIAMS; GM 35939; GM; NIGMS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Adherence of selected strains of coagulase-negative staphylococci to various biomaterials, and the inhibition of their **adherence** by extracellular slime obtained from the **RP12** strain of **Staphylococcus epidermidis** were studied in vitro. **S. epidermidis RP12** adhered considerably more to polymethylmethacrylate (PMMA) discs than did the SP2 strain of **S. hominis** and the SE-360 strain of **S. hyicus**. Strain **RP12** was less **adherent** to titanium alloy, ultrahigh molecular weight polyethylene (UHMWPE), and Teflon discs than to PMMA discs. Exposure of PMMA discs to extracellular slime extracted from strain **RP12** greatly reduced **adherence** of strain **RP12**, SP2, SE-360, and **S. epidermidis** RP-62A. The active component(s) was present in the > 10 kD mol wt fraction obtained by Amicon YM10 ultrafiltration of crude slime; heat treatment of the fraction did not affect its inhibitory activity. When the bacteria and **RP12** slime fractions were added simultaneously to the PMMA discs, the > 10 kD mol wt fraction of slime competitively inhibited **adherence** of strain **RP12** to PMMA discs; in contrast, the < 10 kD mol wt fraction enhanced **adherence** of strain **RP12** to PMMA discs.

Tags: Comparative Study; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Bacterial **Adhesion** --drug effects--DE; *Bacterial Capsules --pharmacology--PD; *Biocompatible Materials; *Methylmethacrylates; ***Staphylococcus epidermidis**--physiology--PH; *Titanium; Bacterial Capsules --chemistry--CH; Species Specificity; **Staphylococcus epidermidis** --chemistry--CH; Temperature

CAS Registry No.: 0 (Bacterial Capsules); 0 (Biocompatible Materials); 0 (Methylmethacrylates); 12743-70-3 (titanium alloy (TiAl6V4)); 7440-32-6 (Titanium)

Record Date Created: 19950223

Record Date Completed: 19950223

13/9/5

DIALOG(R) File 155:MEDLINE(R)

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10743399 PMID: 7948583

Site-specific adhesion of Staphylococcus epidermidis (RP12) in Ti-Al-V metal systems.

Gabriel B L; Gold J; Gristina A G; Kasemo B; Lausmaa J; Harrer C; Myrvik Q N

James Madison University, Harrisonburg, VA 22801.

Biomaterials (ENGLAND) Jun 1994, 15 (8) p628-34, ISSN 0142-9612

Journal Code: 8100316

Contract/Grant No.: AR26957; AR; NIAMS; GM35939; GM; NIGMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS

Staphylococcus epidermidis (RP12) adhesion patterns were studied on the following titanium (Ti)-aluminium (Al)-vanadium (V) metal systems: (i) microfabricated samples consisting of Ti, Al and V islands deposited onto Ti or V substrata, (ii) pure Ti, Al and V metals, and (iii) medical grade Ti6Al4-V alloy. All of these surfaces were covered with their respective oxides formed upon exposure of the metals to air. Quantitative analysis of the number of cells bound per unit area indicates that *S. epidermidis* (**RP12**) exhibits greatest **adhesion** to pure V surfaces. When exposed to surfaces having controlled spatial variations in chemical composition on the 10 microns scale (microfabricated samples), the bacteria preferentially populate V islands versus Ti or Al substrata. In the case of the biphasic Ti6Al4V alloy, the bacteria tend to **adhere** to V-rich, mixed phase regions and phase boundaries. These findings demonstrate that enhanced and preferential **adhesion** of *S. epidermidis* (**RP12**) occurs on V surfaces in Ti-Al-V metal systems and suggest that bacterial interactions are influenced by surface oxide composition.

Tags: Comparative Study; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Bacterial **Adhesion** ; *Biocompatible Materials; ***Staphylococcus epidermidis**; *Titanium; Microscopy, Electron, Scanning
CAS Registry No.: 0 (Biocompatible Materials); 12743-70-3 (titanium alloy (TiAl6V4)); 7440-32-6 (Titanium)
Record Date Created: 19941206
Record Date Completed: 19941206

13/9/6

DIALOG(R) File 155:MEDLINE(R)

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10305852 PMID: 8399955

Altered oxidative responses and antibacterial activity of adult rabbit alveolar macrophages exposed to poly(methyl methacrylate).

Giridhar G; Gristina A G; Myrvik Q N

Medical Sciences Research Institute, Herndon, VA 22071.

Biomaterials (ENGLAND) Jul 1993, 14 (8) p609-14, ISSN 0142-9612

Journal Code: 8100316

Contract/Grant No.: GM 35939; GM; NIGMS; HL 31624; HL; NHLBI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

The effect of poly(methyl methacrylate) (PMMA) on the oxidative responses and antibacterial activity of adult rabbit alveolar macrophages (AM) was studied. PMMA beads (ca. 0.3 micron diameter) elicited an acute respiratory burst within 6-8 min after the addition of the beads. In contrast. Teflon beads of comparable size (ca. 0.2 micron diameter) did not elicit an oxidative burst of AM. An oxidative response was elicited only by those PMMA samples that had affinity for AM **adherence**. Incubation of AM with PMMA beads reduced the subsequent phorbol myristate acetate (PMA)-elicited

oxidative burst by more than 80%. The **Staphylococcus epidermidis**-- **RP12** killing capacity of AM was greatly increased when PMMA beads (ca. 0.3 micron) were added to the challenge dose of bacteria. Pre-incubation of freshly harvested AM with PMMA beads, which greatly reduced subsequent PMA-elicited chemiluminescent (CL) responses did not significantly affect the **RP12** killing capacity of AM. Our data also suggest that killing of the **RP12** strain of *S. epidermidis* does not involve reactive oxygen intermediates.

Tags: Female; Male; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Macrophages, Alveolar--drug effects--DE; *Macrophages, Alveolar--physiology--PH; *Methylmethacrylates--pharmacology--PD; Animals; Cell **Adhesion** --drug effects--DE; Macrophages, Alveolar--metabolism--ME; Oxidation-Reduction; Rabbits; Respiratory Burst--drug effects--DE; **Staphylococcus epidermidis**--physiology--PH; Surface-Active Agents --pharmacology--PD

CAS Registry No.: 0 (Methylmethacrylates); 0 (Surface-Active Agents)

Record Date Created: 19931028

Record Date Completed: 19931028

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S3	1938	E1-E8
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S9	320	(S2 OR S3) AND (S4 OR S5 OR S6 OR S7 OR S8)
S10	0	S9 AND (RP12 OR LD1 OR SP2 OR 35983)
S11	35	'RP12'
S12	7	(S2 OR S3) AND S11
S13	6	S12 AND (ADHESION? OR ADHESIN? OR ADHER? OR ATTACH? OR COL- ONI?)

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98 S15

69243 S2

1938 S3

S16 23 S15 AND (S2 OR S3)

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275 S4

208 S5

298 S6

1227 S7

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10305852 PMID: 8399955

Altered oxidative responses and antibacterial activity of adult rabbit alveolar macrophages exposed to poly(methyl methacrylate).

Giridhar G; Gristina A G ; Myrvik Q N

Medical Sciences Research Institute, Herndon, VA 22071.

Biomaterials (ENGLAND) Jul 1993, 14 (8) p609-14, ISSN 0142-9612

Journal Code: 8100316

Contract/Grant No.: GM 35939; GM; NIGMS; HL 31624; HL; NHLBI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

The effect of poly(methyl methacrylate) (PMMA) on the oxidative responses and antibacterial activity of adult rabbit alveolar macrophages (AM) was studied. PMMA beads (ca. 0.3 micron diameter) elicited an acute respiratory burst within 6- 8 min after the addition of the beads. In contrast. Teflon beads of comparable size (ca. 0.2 micron diameter) did not elicit an oxidative burst of AM. An oxidative response was elicited only by those PMMA samples that had affinity for AM adherence. Incubation of AM with PMMA beads reduced the subsequent phorbol myristate acetate (PMA)-elicited oxidative burst by more than 80%. The *Staphylococcus epidermidis*--RP12 killing capacity of AM was greatly increased when PMMA beads (ca. 0.3 micron) were added to the challenge dose of bacteria. Pre-incubation of freshly harvested AM with PMMA beads, which greatly reduced subsequent PMA-elicited chemiluminescent (CL) responses did not significantly affect the RP12 killing capacity of AM. Our data also suggest that killing of the RP12 strain of *S. epidermidis* does not involve reactive oxygen intermediates.

Tags: Female; Male; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Macrophages, Alveolar--drug effects--DE; *Macrophages, Alveolar--physiology--PH; *Methylmethacrylates--pharmacology--PD; Animals; Cell Adhesion--drug effects--DE; Macrophages, Alveolar--metabolism--ME; Oxidation-Reduction; Rabbits; Respiratory Burst--drug effects--DE; *Staphylococcus epidermidis*--physiology--PH; Surface-Active Agents--pharmacology--PD

CAS Registry No.: 0 (Methylmethacrylates); 0 (Surface-Active Agents)

Record Date Created: 19931028

Record Date Completed: 19931028

17/9/2

DIALOG(R) File 155:MEDLINE(R)
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08702081 PMID: 2765629

In vitro and in vivo comparative colonization of Staphylococcus aureus and Staphylococcus epidermidis on orthopaedic implant materials.

Barth E; Myrvik Q M; Wagner W; Gristina A G

Section of Orthopedic Surgery, Bowman Gray School of Medicine, Wake Forest University Medical Center, Winston-Salem, NC 27103.

Biomaterials (ENGLAND) Jul 1989, 10 (5) p325-8, ISSN 0142-9612

Journal Code: 8100316

Contract/Grant No.: GM 35939-02; GM; NIGMS

Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS

Clinically, **Staphylococcus aureus** appears to be the dominant organism associated with infected metal implants, whereas coagulase-negative staphylococcal strains are more frequently isolated from infected polymer implants. We reproduced this trend experimentally in vitro and in vivo. Discs of a titanium alloy, poly(methyl methacrylate) and ultra-high molecular weight polyethylene were exposed to a clinical isolate of **Staphylococcus aureus** or either of two strains of **Staphylococcus epidermidis**. Within 1 h **Staphylococcus aureus** was always the most rapid colonizer regardless of biomaterial. However, after 8 to 24 h, **Staphylococcus aureus** was present in higher numbers on metal and **Staphylococcus epidermidis** on polymers. Moreover, the exopolysaccharide produced by **Staphylococcus epidermidis** appeared to offer an effective protection against host defences in vivo.

Tags: Comparative Study; Male; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Biocompatible Materials--adverse effects--AE; ***Staphylococcus aureus**--growth and development--GD; ***Staphylococcus epidermidis**--growth and development--GD; Alloys; Animals; Bacterial Adhesion; Materials Testing; Polymers; Prostheses and Implants--adverse effects--AE; Rabbits; Staphylococcal Infections--etiology--ET; **Staphylococcus aureus**--cytology--CY; **Staphylococcus epidermidis**--cytology--CY; Titanium

CAS Registry No.: 0 (Alloys); 0 (Biocompatible Materials); 0 (Polymers); 12743-70-3 (titanium alloy (TiAl6V4)); 7440-32-6 (Titanium)

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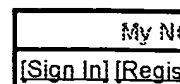
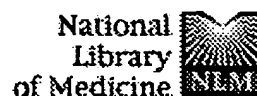
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Staphylococcus epidermidis adhesion to hydrophobic biomedical polymer is mediated by platelets.

Wang IW, Anderson JM, Marchant RE.

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio 44106.

A quantitative investigation on the effects of plasma proteins and platelets on the adhesion of *Staphylococcus epidermidis* RP62A to a hydrophobic biomedical polymer (National Heart, Lung, and Blood Institute reference polyethylene) was carried out under well-defined shear conditions approximating human blood circulation by using a rotating disk system. The results showed that contact-activated platelets mediated *S. epidermidis* adhesion to the polymer surface. In the range of physiologic shear conditions, the adhesive coefficient (ratio of bacteria per unit area to the product of bacterial flux and the duration of the experiment) to platelets was significantly greater than to the protein-adsorbed polyethylene surface by at least one order of magnitude ($P < \text{or} = .01$). The presence of absorbed plasma proteins on polyethylene reduced the adhesion of *S. epidermidis* compared with that seen with the bare polymer surface. These studies show that *S. epidermidis* adhesion to polyethylene is mediated by contact-activated platelets, not absorbed plasma proteins.

PMID: 8421167 [PubMed - indexed for MEDLINE]

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L1: Entry 1 of 1

File: USPT

Jan 11, 2005

US-PAT-NO: 6841154

DOCUMENT-IDENTIFIER: US 6841154 B2

TITLE: Cross-reactive monoclonal and polyclonal antibodies which recognize surface proteins from coagulase-negative staphylococci and Staphylococcus aureus

DATE-ISSUED: January 11, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Foster; Timothy	Dublin			IE
Roche; Fiona	Dublin			IE
Pallen; Mark	Worcs			GB
Patti; Joseph M.	Cumming	GA		
Hutchins; Jeff T.	Cumming	GA		
Speziale; Pietro	Pavia			IT

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE	CODE
Inhibitex, Inc.	Alpharetta	GA				02
The Provost Fellows and Scholars of the College of the Holy and Undivided Trinity of Queen Elizabeth Near Dublin	Dublin			IE		03
Universita'degli Studi di Pavia	Pavia			IT		03

APPL-NO: 10/ 172502 [PALM]

DATE FILED: June 17, 2002

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. provisional application Ser. No. 60/298,098 filed Jun. 15, 2001.

INT-CL: [07] A61 K 39/40

US-CL-ISSUED: 424/165.1; 424/164.1, 530/387, 530/388.1, 530/388.15, 530/387.3, 530/387.9, 530/388.4

US-CL-CURRENT: 424/165.1; 424/164.1, 530/387.1, 530/387.3, 530/387.9, 530/388.1, 530/388.15, 530/388.4

FIELD-OF-SEARCH: 424/165.1, 424/164.1, 530/387.1, 530/388.1, 530/388.15, 530/387.3, 530/387.9, 530/388.4

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
<input type="checkbox"/> 4816567	March 1989	Cabilly et al.	
<input type="checkbox"/> 5175096	December 1992	Hook et al.	
<input type="checkbox"/> 5320951	June 1994	Hook et al.	
<input type="checkbox"/> 5416021	May 1995	Hook et al.	
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<input type="checkbox"/> 5707702	January 1998	Brady, Jr. et al.	
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<input type="checkbox"/> 5807715	September 1998	Morrison et al.	
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<input type="checkbox"/> 5981216	November 1999	Kenten et al.	
<input type="checkbox"/> 6008341	December 1999	Foster et al.	
<input type="checkbox"/> 6086895	July 2000	Hook et al.	
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<input type="checkbox"/> 6288214	September 2001	Hook et al.	
<input type="checkbox"/> 6294177	September 2001	Fattom	424/243.1
<input type="checkbox"/> 6331415	December 2001	Cabilly et al.	

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
O 519 596	December 1992	EP	
WO 97/48727	December 1997	WO	
WO 00/12689	March 2000	WO	
WO 00/71585	November 2000	WO	

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Novel Iron-Regulated . . . ", Infection and Immunity, Aug. 1998, pp. 3767-3774.
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Mazmanian et al., "Sortase-catalysed anchoring of surface proteins to the cell wall of Staphylococcus aureus", MicroReview, Molecular Microbiology (2001), 40(5), 1049-1057.

ART-UNIT: 1645

PRIMARY-EXAMINER: Graser; Jennifer E.

ATTY-AGENT-FIRM: Stites & Harbison PLLC Schulman; B. Aaron

ABSTRACT:

Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as S. aureus and to coagulase-negative bacteria, such as S. epidermidis and S. hemolyticus, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between S. aureus and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.

11 Claims, 14 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

BRIEF SUMMARY:

1 FIELD OF THE INVENTION

2 The present invention relates in general to surface proteins from Staphylococcus aureus and their active regions such as their A domains which have homologue proteins on coagulase-negative Staphylococci such as S. epidermidis and S. hemolyticus as well as antibodies which recognize said proteins, and in particular to isolated monoclonal and polyclonal antibodies which recognize specific proteins from Staphylococcus aureus and coagulase-negative Staphylococci and which are cross-reactive against S. aureus and coagulase-negative Staphylococci and can thus be utilized in vaccines and methods useful for preventing or treating a wide variety of infections caused by staphylococcal bacteria.

3 BACKGROUND OF THE INVENTION

4 The successful colonization of the host is a process required for most

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13635688 Genuine Article#: 901GU Number of References: 40
Title: Inhibition of biofilm formation by monoclonal antibodies against Staphylococcus epidermidis RP62A accumulation-associated protein
Author(s): Sun DQ; Accavitti MA; Bryers JD (REPRINT)
Corporate Source: Univ Washington, Dept Bioengn, 466A Bagley Hall, POB 351720/Seattle//WA/98195 (REPRINT); Univ Connecticut, Dept Chem Engn, Storrs//CT/; Univ Connecticut, Ctr Hlth, Ctr Biomat, Farmington//CT/; Univ Alabama, Hybridoma Phage Display Core Facil, Huntsville//AL/35899(jbryers@u.washington.edu)
Journal: CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, 2005, V12, N1 (JAN), P93-100
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Geographic Location: USA
Journal Subject Category: IMMUNOLOGY; INFECTIOUS DISEASES; MICROBIOLOGY
Abstract: Staphylococcus epidermidis expresses a 140-kDa cell wall-bound protein accumulation-associated protein (AAP) to adhere to and accumulate as a biofilm on a surface. Potentially blocking AAP with a monoclonal antibody (MAb) could reduce or eliminate S. epidermidis bacterial colonization of biomedical devices. Here, we report on our efforts to (i) isolate AAP, (ii) generate MAbs against AAP, and (iii) determine the efficacy of MAbs to inhibit S. epidermidis biofilm formation. An M7 S. epidermidis mutant, reportedly deficient in AAP expression, was used as a negative control. Postinoculation murine sera, containing polyclonal antibodies against AAP, were able to reduce S. epidermidis biofilm formation by 54%. Select MAbs against AAP were able to reduce S. epidermidis by no more than 66%. Two MAb mixtures, 12C6/12A1 and 3C1/12A1, reduced S. epidermidis accumulation up to 79 and 87%, respectively, significantly more than individual MAbs. Contrary to a previous report, biofilm-deficient S. epidermidis mutant M7 expressed a 200-kDa protein on its cell wall that specifically bound AAP MAbs. Peptide characterization of this M7 protein by microcapillary reversed-phase high-pressure liquid chromatography-nanoelectrospray tandem mass spectrometry resulted in 53% homology with AAP. Ongoing studies will elucidate the dynamic expression of AAP and the M7 200-kDa protein in order to define their roles in biofilm formation.
Identifiers--Keyword Plus(R): **FIBRINOGEN - BINDING -PROTEIN; CAPSULAR POLYSACCHARIDE/ADHESIN; PSEUDOMONAS-AERUGINOSA; PASSIVE-IMMUNIZATION; ANTIGEN-BINDING; ADHESION; GENE; IMMUNOGLOBULINS; IDENTIFICATION;**

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6/9/2 (Item 2 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci

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10314860 Genuine Article#: 512HU Number of References: 51

Title: Teichoic acid enhances adhesion of Staphylococcus epidermidis to immobilized fibronectin

Author(s): Hussain M (REPRINT) ; Heilmann C; Peters G; Herrmann M

Corporate Source: Univ Hosp Muenster, Inst Med Microbiol, Munster//Germany/
(REPRINT); Univ Hosp Muenster, Inst Med Microbiol, Munster//Germany/

Journal: MICROBIAL PATHOGENESIS, 2001, V31, N6 (DEC), P261-270

ISSN: 0882-4010 Publication date: 20011200

Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND

Language: English Document Type: ARTICLE

Geographic Location: Germany

Journal Subject Category: IMMUNOLOGY; MICROBIOLOGY

Abstract: Adhesion is a prerequisite for coagulase-negative staphylococci to cause invasive disease and may be mediated by adhesive host molecules adsorbed on implanted polymers. In this study, we can confirm previous observations demonstrating binding of *Staphylococcus epidermidis* to fibronectin (FN) adsorbed polymer surfaces. So far, the nature of FN-recognizing adhesin(s) in *S. epidermidis* remains elusive. Since teichoic acids (TA) have been shown to exert binding functions for extracellular matrix molecules in several Gram-positive species, we have purified wall TA of *S. epidermidis* laboratory strains KH11 and **RP62A**, as well as clinical isolate AB9. Using a polymethylmethacrylate (PMMA) coverslip adhesion assay, a microtitre plate assay and a particle agglutination assay, we found that purified TA significantly enhanced adhesion of *S. epidermidis* KH11 and **RP62A** to FN coated surfaces. Enhanced adhesion was dose-dependent and saturable. Preincubation, either of microorganisms or of FN coated surfaces, with TA promoted adhesion, while adhesion to TA-adsorbed PMMA was comparably low. This observation may suggest a potential role of cell wall carbohydrates as bridging molecules between microorganisms and immobilized FN in early steps of *S. epidermidis* pathogenesis. (C) 2001 Academic Press.

Descriptors--Author Keywords: *Staphylococcus epidermidis* ; bacterial adhesion ; fibronectin ; teichoic acid

Identifiers--KeyWord Plus(R): COAGULASE-NEGATIVE STAPHYLOCOCCI; INTERCELLULAR-ADHESION; EXTRACELLULAR SLIME; LIPOTEICHOIC ACID; **ADHERENCE**; **FIBRINOGEN**; PROTEIN; AUREUS; SURFACES; STRAINS

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6/9/3 (Item 3 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
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06756321 Genuine Article#: ZP714 Number of References: 31

Title: The abilities of a Staphylococcus epidermidis wild-type strain and its slime-negative mutant to induce endocarditis in rabbits are comparable

Author(s): PerdreauRemington F (REPRINT) ; Sande MA; Peters G; Chambers HF
 Corporate Source: UNIV CALIF SAN FRANCISCO, SAN FRANCISCO GEN HOSP, MED
 SERV, 1001 POTRERO AVE, BLDG 100, ROOM 301/SAN FRANCISCO//CA/94110
 (REPRINT); UNIV COLOGNE, INST MED MICROBIOL & HYG/D-5000
 COLOGNE//GERMANY//; UNIV MUNSTER, INST MED MICROBIOL & HYG/D-4400
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Journal: INFECTION AND IMMUNITY, 1998, V66, N6 (JUN), P2778-2781

ISSN: 0019-9567 Publication date: 19980600

Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
 WASHINGTON, DC 20005-4171

Language: English Document Type: ARTICLE

Geographic Location: USA; GERMANY

Subfile: CC LIFE--Current Contents, Life Sciences

Journal Subject Category: IMMUNOLOGY; INFECTIOUS DISEASES

Abstract: The abilities of a parent and mutant pair of Staphylococcus epidermidis strains, the slime-producing parent **RP62A** and its slime-negative mutant, to establish endocarditis in a rabbit model of aortic valve endocarditis and to accumulate and adhere to surfaces in vitro were compared. Vegetation titer and infection rate depended on the presence or absence of a catheter ($P = 0.020$) and on inoculum size ($P < 0.001$) but not on the infecting strain. The ability of the parent strain vis-g-vis its mutant to accumulate in vitro on surfaces as demonstrated in a slime test did not correlate with any enhancement in the development of endocarditis in the rabbit model. In vitro initial adherence rates were identical. Both isolates accumulated to the same reduced extent in vitro in the presence of serum, albumin, or gelatin. Adhesion was equally promoted by addition of fibronectin. These data suggest that the in vitro phenomenon of accumulation described as slime production in the absence of serum may not be an important virulence determinant in vivo.

Identifiers--KeyWord Plus(R): INFECTIONS; ADHERENCE; FIBRONECTIN; SURFACES;
COLONIZATION; ASSOCIATION; **FIBRINOGEN**; CATHETERS; **ADHESION**; SHUNTS

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6/9/4 (Item 4 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci

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04261955 Genuine Article#: RT108 Number of References: 40

**Title: BIOMATERIAL-ASSOCIATED STAPHYLOCOCCAL PERITONEAL INFECTIONS IN A
NEUTROPAENIC MOUSE MODEL**

Author(s): ROZALSKA B; LJUNGH A

Corporate Source: LUND UNIV,DEPT MED MICROBIOL,SOLVEGATAN 23/S-22362

LUND//SWEDEN/; LUND UNIV,DEPT MED MICROBIOL/S-22362 LUND//SWEDEN/; UNIV
LODZ,INST MICROBIOL,DEPT INFECT BIOL/PL-90131 LODZ//POLAND/

Journal: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, 1995, V11, N4 (JUL), P
307-319

ISSN: 0928-8244

Language: ENGLISH Document Type: ARTICLE

Geographic Location: SWEDEN; POLAND

Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences

Journal Subject Category: IMMUNOLOGY; MICROBIOLOGY

Abstract: Adhesion of staphylococcal cells to polyethylene with end
point-attached heparin was quantified by bioluminescence.

Staphylococcus epidermidis 3380 and the slime-producing S. epidermidis
RP12 adhered to the highest extent, and S. lugdunensis 2342 to the
least extent. Preincubation of the polymer with dialysis fluid reduced

adhesion of *S. epidermidis* 3380 and **RP12** but enhanced that of *S. aureus*, and preadsorption of the surface with fibronectin decreased subsequent adhesion of *S. epidermidis* and *S. haemolyticus* strains. When staphylococci were grown in the presence of a biomaterial their ability to activate peritoneal cells was decreased. The bactericidal activity was impaired, whereas ingestion of opsonized coagulase-negative staphylococci (CNS) strains was unaffected. With *S. epidermidis* **RP12** the presence of biomaterial did not influence either phagocytosis or bactericidal effect of peritoneal cells. After intra-peritoneal challenge with staphylococcal strains, the organ uptake of *S. aureus* Cowan 1 was increased in normal mice whereas immunosuppressed mice died. CNS strains increased mainly in the peritoneal cavity of immunosuppressed mice. The uptake of bacteria in liver and kidneys was increased with *S. epidermidis* 3380, *S. lugdunensis* 2343 and *S. schleiferi* 667-88. Generally, CNS strains persisted in the peritoneal cavity of both normal and immunosuppressed mice. These data indicate that host defense mechanisms, mainly polymorphonuclear neutrophils, fail to eliminate CNS infections in the peritoneum, and that initial adhesion to an implanted biomaterial may be of lesser importance in the peritoneal cavity than in e.g. catheter-associated infections. There are strain-specific virulence factors of bacteria, and slime producing strains evade the host defense mechanisms more efficiently than non-slime producing strains.

Descriptors--Author Keywords: PERITONEAL INFECTION ; HEPARINIZED POLYETHYLENE FIBRONECTIN NEUTROPHIL PHAGOCYTOSIS ; NEUTROPAENIC MOUSE MODEL ; STAPHYLOCOCCUS

Identifiers--KeyWords Plus: COAGULASE-NEGATIVE STAPHYLOCOCCI; FOREIGN-BODY INFECTION; ADHERENCE; FIBRONECTIN; EPIDERMIDIS; CATHETERS; DIALYSIS; SURFACES; BINDING; VITRONECTIN

Research Fronts: 93-4051 002 (COAGULASE-NEGATIVE STAPHYLOCOCCI; EXPERIMENTAL FOREIGN-BODY INFECTION IN MICE; INVITRO ACTIVITY)
 93-5223 001 (CENTRAL VENOUS CATHETER-RELATED INFECTIONS; SURFACE ANTIMICROBIAL ACTIVITY; SUBCLAVIAN VEIN STENOSIS)
 93-8293 001 (RECEPTOR-MEDIATED ENDOCYTOSIS OF VITRONECTIN; INTEGRIN EXPRESSION; **FIBRINOGEN BINDING** ; MESANGIAL CELLS; PLASMINOGEN-ACTIVATOR INHIBITOR-1)

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DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
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03899382 Genuine Article#: QP943 Number of References: 39

**Title: ADHESION OF STAPHYLOCOCCUS-EPIDERMIDIS TO BIOMEDICAL POLYMERS -
 CONTRIBUTIONS OF SURFACE THERMODYNAMICS AND HEMODYNAMIC SHEAR
 CONDITIONS**

Author(s): WANG IW; ANDERSON JM; JACOBS MR; MARCHANT RE

Corporate Source: CASE WESTERN RESERVE UNIV,DEPT BIOMED

ENGN/CLEVELAND//OH/44106; CASE WESTERN RESERVE UNIV,DEPT BIOMED

ENGN/CLEVELAND//OH/44106; CASE WESTERN RESERVE UNIV,DEPT MACROMOLEC

SCI/CLEVELAND//OH/44106; CASE WESTERN RESERVE UNIV,INST

PATHOL/CLEVELAND//OH/44106

Journal: JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, 1995, V29, N4 (APR), P
 485-493

ISSN: 0021-9304

Language: ENGLISH Document Type: ARTICLE

Geographic Location: USA

Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences

Journal Subject Category: ENGINEERING, BIOMEDICAL; MATERIALS SCIENCE,
 BIOMATERIALS

Abstract: Adhesion studies of Staphylococcus epidermidis **RP62A** were conducted using a rotating disk system to determine the roles of surface physicochemistry and topographies under physiologic shear conditions. Six materials were investigated: biomedical reference polyethylene and polydimethylsiloxane; argon plasma-treated reference polyethylene (Ar-PE); Silastic(R); expanded polytetrafluoroethylene; and woven Dacron. All of the polymers except Dacron demonstrated reduced bacterial adhesion with increasing shear stress. Argon plasma treatment of polyethylene reduced the level of staphylococcal adhesion. Adsorption of human plasma proteins effected significantly lower numbers of adherent bacteria. The lowest adhesion was observed for Ar-PE in 1% human plasma protein solution, whereas Dacron had the highest number of adherent bacteria. The high adhesion on Dacron was attributed to increased bacterial flux caused by topography-induced turbulent flow and physical entrapment of the bacteria in the fiber interstices. The results indicate that the driving force for S. epidermidis adhesion is strongly influenced by substrate

physicochemistry, but this may be dominated by physical forces such as shear and turbulence. (C) 1995 John Wiley & Sons, Inc.
Identifiers--KeyWords Plus: PROSTHETIC VASCULAR GRAFTS; PLASMA-PROTEINS;
ADHERENCE; BIOMATERIALS; FIBRONECTIN; **FIBRINOGEN**; PRINCIPLES;
ADSORPTION; ALBUMIN

Research Fronts: 93-4051 001 (COAGULASE-NEGATIVE STAPHYLOCOCCI;
EXPERIMENTAL FOREIGN-BODY INFECTION IN MICE; INVITRO ACTIVITY)

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\$0.05 Estimated cost File155
\$0.09 0.015 DialUnits File5
\$0.09 Estimated cost File5
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\$32.15 5 Type(s) in Format 9
\$32.15 5 Types
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\$0.06 0.015 DialUnits File35
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Other Reference Publication (4):

McDevitt et al., "Molecular characterization of the clumping factor (fibrinogen receptor) of *Staphylococcus aureus*", *Molecular Microbiology*, 1994, 11(2) pp. 237-248.

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McCrea et al., "A Family of Putative Adherence Proteins Related to the Clumping Factor of *Staphylococcus aureus*", *Abstracts of the General Meeting of the American Society for Microbiology* (1998), vol. 98, p. 63.

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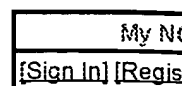
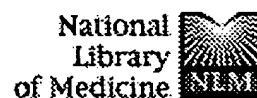
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Early adhesion of bacteremic strains of *Staphylococcus epidermidis* to polystyrene: influence of hydrophobicity, slime production, plasma, albumin, fibrinogen, and fibronectin.

Galliani S, Viot M, Cremieux A, Van der Auwera P.

Clinique des Maladies Infectieuses, l'Universite Libre de Bruxelles, Belgium.

Twenty bacteremic strains of *Staphylococcus epidermidis* were characterized according to their hydrophobicity, their ability to produce slime, and their in vitro adhesion to polystyrene microtiter plates precoated or not with plasma proteins. Four strains of *Staphylococcus aureus* were also tested for adhesion. Slime production in *S. epidermidis* was not correlated with initial adhesion, whether measured qualitatively or by a quantitative method. Hydrophobicity (xylene:water partition) was well correlated with adhesion. Slime production, adhesion, and hydrophobicity were highly strain dependent among *S. epidermidis* organisms. For *S. epidermidis*, early adhesion was inhibited (10% to 98%) by albumin and fibronectin in all strains, by plasma (19 strains), and by fibrinogen (18 strains). Stimulation occurred for one strain with plasma and two strains with fibrinogen. In contrast, adhesion was inhibited by albumin and markedly stimulated (twofold to 14-fold) by plasma, fibrinogen, and fibronectin for the four strains of *S. aureus*. Early adhesion of *S. epidermidis* to polymer surface appears to depend mainly on hydrophobicity and is usually impaired by plasma proteins, albumin, fibrinogen and fibronectin; with a heterogeneous behavior among the different strains tested. Slime production would interpose secondarily, after the first attachment.



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Adhesion of coagulase-negative staphylococci and adsorption of plasma proteins to heparinized polymer surfaces.

Yu J, Montelius MN, Paulsson M, Gouda I, Larm O, Montelius L, Ljungh A.

Department of Medical Microbiology, University of Lund, Sweden.

Protease treatment of cells of coagulase-negative staphylococci reduced the adhesion of bacteria to heparinized polyethylene preadsorbed with serum. Fibronectin (Fn), fibrinogen (Fg), vitronectin, complement factor C3c, plasminogen, laminin and to a low extent albumin were detected on tridodecylmethylammonium chloride (TDMAC)-heparinized polyvinyl chloride (PVC) catheters extirpated from the circulation of patients. Using a perfusion model we show that during the first hours of perfusion with human plasma, Fn and Vn dominate, whereas after 22 h of perfusion Fg is the dominant protein. Field emission scanning electron microscopy and atomic force microscopy studies on TDMAC-heparinized catheters as well as on end-point attached heparinized PVC catheters indicate that quantitatively more Fg than Fn is exposed on these surfaces after prolonged exposure (> 22 h) to human plasma.

PMID: 7986945 [PubMed - indexed for MEDLINE]

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